

Short stature/short limb skeletal dysplasia with severe combined immunodeficiency and bowing of the femora: report of two patients and review

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Abstract

We report two patients with severe combined immunodeficiency and short stature/short limb skeletal dysplasia. Case 1 presented at birth with rhizomelic shortening of the extremities and bowing of the femora. She developed clinical signs of severe combined immunodeficiency at 13 months and died at 21 months. Case 2 had severe prenatal shortening and bowing of the extremities and a small, malformed chest. Symptoms of severe combined immunodeficiency and severe failure to thrive developed soon after birth and she died at 5 months.

The diagnosis of severe combined immunodeficiency in our patients was based on their clinical course and necropsy findings, supported in case 1 by the results of immune function tests. The results of investigation of immune function (immunoglobulins, lymphocyte subpopulations, lymphocyte function) are very variable in this syndrome as in other variants of severe combined immunodeficiency. Bone histopathology in both patients showed grossly irregular costochondral junctions, but normal transition of proliferating to hypertrophic chondrocytes. These cases belong to early lethal type 1 short limb skeletal dysplasia with severe combined immunodeficiency.

Review of previously published cases with severe

combined immunodeficiency and well documented skeletal findings show eight patients with prenatal onset of bowing and shortening of the extremities and metaphyseal abnormalities. These include two sib pairs concordant for the skeletal changes. In these cases, adenosine deaminase levels were not reported. An additional four published cases with associated adenosine deaminase deficiency had only mild metaphyseal abnormalities, but subsequently showed no linear growth. As adenosine deaminase levels were not determined in cases with severe short limb skeletal dysplasia, no conclusion can be reached as to whether associated adenosine deaminase deficiency is a constant feature of this syndrome or whether cases with adenosine deaminase deficiency present with milder skeletal changes.

This rare autosomal recessive syndrome should be included in the list of skeletal dysplasias presenting with shortening and bowing of the long bones and metaphyseal abnormalities and in the WHO classification of combined immunodeficiencies with other major defects.

The clinical entity of variable degrees of immunodeficiency associated with short limb skeletal dysplasia and autosomal recessive inheritance has been recognised for over 20 years. In 1965, McKusick *et al*¹ defined the syndrome of cartilage-hair hypoplasia (CHH) associated with chronic neutropenia, abnormal cellular immunity, and survival to early childhood. Subsequently, Davis² and McKusick and Cross³ each reported a patient with severe immunodeficiency and 'achondroplasia' who both died in early infancy. Both patients showed severe limb shortening at birth, but had normal facies and skull x ray. A sib of one of these cases was similarly affected.

The previously reported cases have been divided into three categories by Ammann *et al*⁴ according to the type of immunodeficiency present. Type 1 comprises early lethal short limb skeletal dysplasia (SLSD) with severe combined antibody and cell mediated immunodeficiency (SCID); associated adenosine deaminase deficiency (ADA) was described

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Table 1 Clinical findings and results in 19 cases with severe combined immunodeficiency and short limb skeletal dysplasia (type 1).

Case and reference	Radiology							Immunology	Age at presentation	Death
	Metaphyseal long bones	Chondrodysplasia ribs	Long bones		Broad pelvis	SCID	ADA			
			Bowing	Shortening						
Female ²	-	-	+	+	NR	+	NR	+	3/52	8/52
Female ⁵	+	(Pectus excavatum)	+	+	+	+	NR	+	4/12	6/12
Female {Sibs ³	NR	NR	NR	+	NR	+	NR	NR	Birth	4/12
Male {Sibs ³	+	-	-	+	+	+	NR	NR	Birth	4/12
Male (case 1)	+	+	+	+	+	+	NR	NR	4/12	5/12
Female (case 2)	+	(Pectus excavatum)	+	+	+	+	NR	+	2/12	7/12
This report										
Female (case 1)	Mild	-	+	+	-	+	NR	+	13/12	21/12
Female (case 2)	+	+	+	NR	NR	+	NR	NR	5/12	9/12
Male (case 1) ⁷	Mild	+	-	(No growth)	(Thick growth arrest line)	+	-	+	11 days	9/12
Male (case 2)	NR	+	NR	NR	NR	+	-	+	3/52	10/52
Female (case 3) ⁷	Mild	+	-	(No growth)	(Thick growth arrest lines)	+	(?)	+	6/52	4/12
Male ⁸	+	+	-	NR	NR	+	-	+	7/52	9/52
7 cases ⁹	-	+(6pts)	-	NR	NR	+	-	+	NR	NR
					(Thick growth arrest lines) (3 pts)					

NR = not reported.

in at least four cases (table 1). This entity is rare and only 15 case reports have been published. Type 2 comprises SLSD with cell mediated immunodeficiency, which includes CHH. This is usually less severe with survival to early childhood and many cases have been reported. Type 3 comprises SLSD with antibody mediated immunodeficiency and survival to late childhood. Only two sibs have been described to date.⁴

The expression of the skeletal abnormalities appears to be variable in type 1. Most cases, but not all, have prenatal onset of short stature with predominantly rhizomelic shortening. There is sometimes bowing of the limbs and radiological changes of mild metaphyseal chondrodysplasia. In types 2 and 3 the proportionate shortening of the extremities appears to be a consistent feature and wide metaphyses are usually evident in the first or second year of life.

Congenital bowing of the long bones (CBLB) most commonly presents with other radiological changes and extraskeletal malformations as a part of known syndromes.¹⁰ Several authors have produced classifications of cases with CBLB^{10 11} according to the location and type of bowing, bone density, associated metaphyseal/epiphyseal abnormalities, and extraskeletal malformations. Our report contains case histories of two new patients with SLSD+SCID and their bone histopathology findings. We have also included the histopathology report from one of the first patients described by Davis² from the same hospital (Hammersmith Hospital).

Case reports

CASE 1

This female patient was the first child of Indian parents who were first cousins. The mother was 26 and father 30 years old when the patient was born. Both parents were healthy and of normal stature. The pregnancy was uneventful and the mother reported active fetal movements. The patient was born at term by normal delivery. Her birth weight was 2600 g (3rd centile), length 41 cm (>2 SD below the mean), OFC 35 cm (50th centile), and arm span 44 cm. She had bilateral rhizomelic shortening of the lower limbs, palpable lateral bowing of the femora, and increased skin folds. The skin also appeared redundant over the humeri. The patient had a normal facial appearance (fig 1) and there were no other abnormal clinical signs. She was alert and feeding well. A maternal hysterosalpingogram was normal, excluding the possibility of fetal deformation secondary to uterine malformation. No diagnosis was made and regular follow up was arranged.

When reviewed at 8 months of age (fig 2), the patient was thriving and in good health, except for a



Figure 1 The appearance of case 1 at 1 month showing bilateral bowing of femora and rhizomelic shortening of extremities.



Figure 2 Case 1 at 8 months. The child is alert and well nourished.

two week history of URTI and subsequent admission to hospital for right upper lobe pneumonia. Her developmental milestones were normal. Rhizomelic shortening of the extremities was evident. Her height was reduced (60 cm; >2 SD below the mean) with disproportionate short limbs (US/LS=1.58, arm span=56 cm) and OFC 43 cm (50th centile). She had received two doses of DTP and polio immunisations with no adverse affects. The patient was well until the age of 1 year when she developed unexplained recurrent pyrexia and at 13 months profuse diarrhoea, which lasted a month. She was admitted to hospital and treated for UTI and streptococcal septicaemia. For the first time, the blood count was abnormal, showing marked anaemia and neutropenia (table 2). On examination, she was pale and had cervical and inguinal lymphadenopathy, little tonsillar tissue, mild hepatomegaly, and palpable tip of the spleen. A patch of depigmented skin was noted around the umbilicus. Chest x ray showed extensive bronchial wall thickening. Investigations at 16 months (table 2) showed severe combined immunodeficiency. The cell numbers, except for CD20 (B cells), were within the normal range, despite an absent PHA response which indicates present but non-functional T lymphocytes. Supportive treatment was instituted with antibiotics and frequent transfusions using irradiated blood. During the pre-BMT (bone marrow transplant) investigation, she developed persistent thrombo-

cytopenia, GI bleeding, lymphopenia, and neutropenia. CMV was isolated in the sputum and urine. Bone marrow biopsy performed at that time showed hypocellularity and absent megakaryocytes. At 19 months she developed reduced visual acuity bilaterally, owing to subretinal and subsequently vitreous haemorrhages. At this stage a mismatched BMT was not considered because of her clinical condition. Further bleeding ensued from the GI tract, for which an unsuccessful hemicolecotomy was performed. She died at 21 months after a subarachnoid haemorrhage.

CASE 2

This female was born on 15.4.66 at 35 weeks after a normal pregnancy and delivery. Family history was unremarkable. Birth weight was 2200 g (10th centile) and length 42 cm (1 SD below the mean). She was noted to have short, bowed long bones and a small, malformed chest with prominent costochondral junctions. Failure to thrive and diarrhoea developed soon after birth. She also had generalised eczema, most severe on the scalp, which remained hairless. Investigations showed severe anaemia (table 2), and on bone marrow biopsy normal distribution of all elements was seen, but with a great excess of eosinophils. Repeated blood transfusions were required for persistently low Hb and gammaglobulin injections were

Table 2 Results of haematological and immunological investigations in cases 1 and 2.

	Case 1 (aged 16 months)	Case 2 (aged 1 month)
Hb	5.5 g/dl (low)	4 g/dl (low)
WBC	$4.1 \times 10^9/l$ (N)	$100 \times 10^9/l$ (N)
Neutrophils	$0.9 \times 10^9/l$ (low)	$3.5 \times 10^9/l$ (N)
Lymphocytes	$3.0 \times 10^9/l$ (N)	$2.3 \times 10^9/l$ (N)
Platelets	$3260 \times 10^9/l$	$3000 \times 10^9/l$ (N)
IgG (total)	5.4 g/l (N)	17.5 g/l (high)*
IgG1	3.2 g/l (N)	
IgG2	<0.04 g/l (low)	
IgG3	0.4 g/l (N)	NR
IgG4	0.12 g/l (N)	
IgM	0.5 g/l (N)	0.12 g/l (N)*
IgA	<0.005 g/l (low)	0.04 g/l (N)*
Lymphocyte differentiation markers	Main specificities	%
CD3	Pan T cell	41
CD4	T helper subset	24
CD8	T suppressor/cytotoxic	19
CD14	Macrophages	33
CD19	B cells	10
CD20	Mature B cells	0
CD57	Natural killer cells	27
HLA-DR	Class II MHC antigen	34
PHA stimulation	Pan T lymphocyte response	0-3.8 (SI) (on 3 occasions)
Candida and Mantoux skin test	no response.	
Poor mixed lymphocyte culture response against parents and 3rd party allogenic cells		NR

N=normal, NR=not reported, CD=cluster of differentiation, PHA=phytohaemagglutinin, SI=stimulation index, *levels extrapolated from a normal serum pool used in 1966 before establishment of an immunoglobulin standard by the WHO.

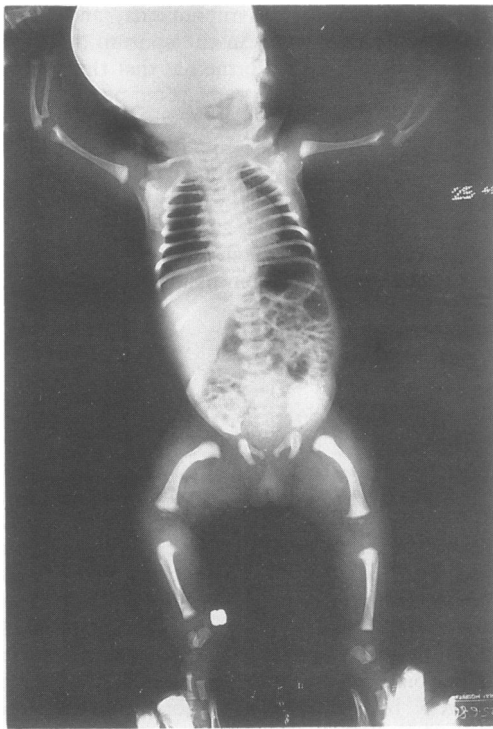


Figure 3 Skeletal x ray of case 1 at birth showing bowing of the femora, absent upper tibial epiphyses, and normal costochondral junctions.

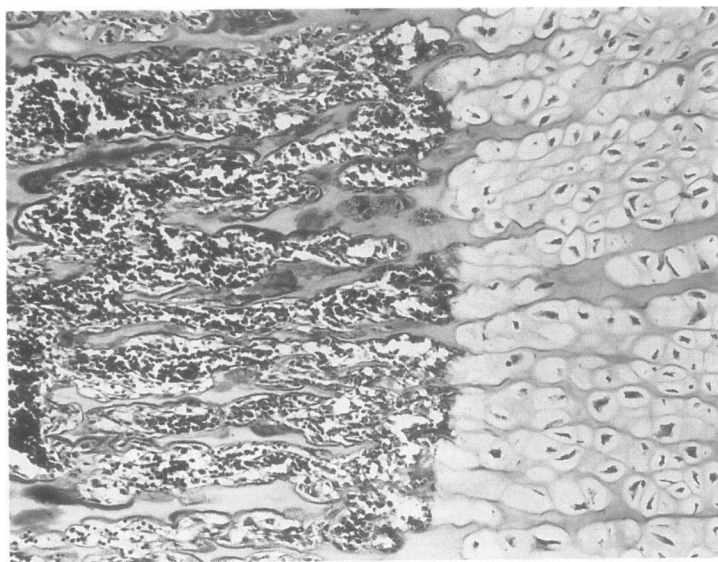
given. No psychomotor development or linear growth was evident and she died at 5 months after the development of abdominal distension and respiratory distress.

Radiology

The radiological findings in both cases are summarised in table 1. In case 1 the upper tibial epiphyses were absent (fig 3), which corresponds to about 28 weeks of gestation and reflects severe localised retardation of bone development. At 18 months the bowing was less severe and early chevron deformities of the lower tibial epiphyses were evident with thin growth arrest lines. The metaphyses of the proximal humeri and the anterior ends of the ribs appeared dense, but not irregular. In case 2, marked bowing and shortening of both femora and humeri was present, with considerable expansion of the epiphyses of these bones and of the costochondral junctions.

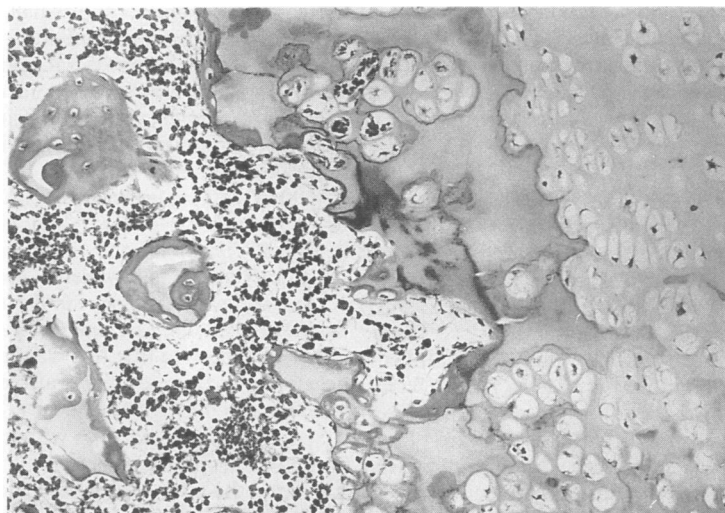
Necropsy

In both cases the necropsy findings were characteristic of a combined immunodeficiency. The thymus was small, Hassall's corpuscles were absent, and there was complete loss of differentiation into cortex and medulla. The spleen and lymph nodes were enlarged and firm. Extensive infiltration by histiocytes, polymorphs, and eosinophils were seen in lymph nodes, which lacked germinal centres. Greatly reduced B cells and T cells in a patchy distribution were seen on immunocytochemical staining. The spleen showed

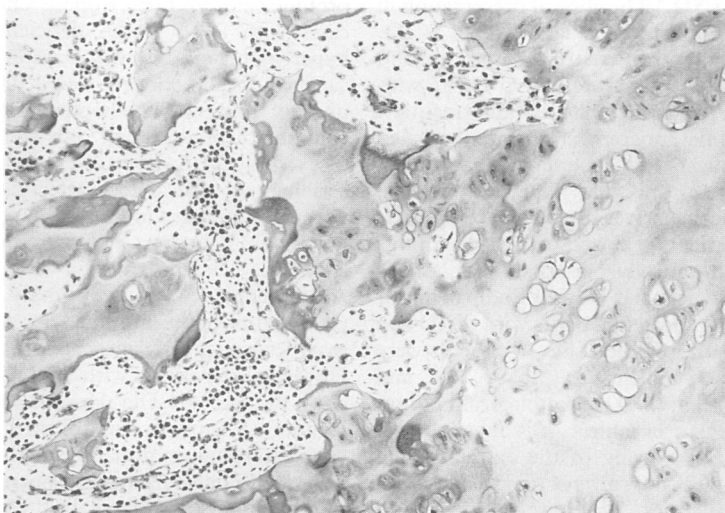


(a)

Figure 4(a) Normal costochondral junction in newborn. Note columns of hypertrophied cartilage cells on the right with persisting intervening matrix which forms trabecula within the metaphysis on the left. (b) Costochondral junction of case 2 showing irregular columns of hypertrophied cartilage cells and impaired capillary ingrowth with poor trabecular formation. Compare with normal in (a). (c) Costochondral junction from case 1 showing islands of persisting cartilage cells extending into partly calcified trabecula.



(b)



(c)

lymphoid depletion of the sinusoids and absence of germinal centres.

The body of case 2 showed generalised emaciation with complete absence of subcutaneous fat; case 1 was unremarkable in that respect. Additional findings in case 2 were non-specific infiltration of the dermis with reticulum cells, eosinophils, and polymorphs, and bilateral internal hydronephrosis.

Bone histopathology

Histopathological examination was carried out on sections from the costochondral junctions and verte-

brae. The findings were similar in both cases but were more marked in case 1. The costochondral junction was grossly irregular when compared with a normal control (fig 4a) and showed lack of alignment of cartilage cells into columns with associated lack of matrix column formation (fig 4b, c). However, the normal transition of proliferating to hypertrophic cells was seen in both cases. There was focal impairment in capillary invasion and extremely poor trabecular formation in the metaphysis. Persisting cartilage cells within islands of matrix extending into the metaphysis were a feature of case 1 (fig 4c). The vertebrae showed similar but less severe changes and the trabeculae

were better developed. Only a section of vertebra was available from the case of Davis.² The histopathological features were identical to those seen in the vertebrae of cases 1 and 2.

Discussion

The diagnosis of SCID in case 1 was based on the findings of reduced T cell numbers, repeatedly absent PHA responses, absence of mature B cells (CD20), but normal numbers of early B cells (CD19). Despite these findings, she had normal total IgG levels, but low IgG2, and IgA levels were depressed. Case 2 had severe anaemia, but normal immunoglobulins. Qualitative tests of immune function in case 2 were not performed, as this patient presented in 1966. The necropsy findings were identical to those of case 1 (see text). Clinical features and necropsy findings in SCID are usually characteristic, while laboratory investigations of immune function and cell numbers show great variability.

The two cases reported here fall into the category of type 1 SCID with SLSD.⁴ The clinical presentation in case 1 was unusual because of the late onset of SCID. Mild rhizomelic shortening of the extremities and bowing of the femora were present at birth with normal bone density and no metaphyseal abnormalities. The diagnosis became apparent at 13 months when she developed clinical and laboratory features of SCID and died at 21 months. The early clinical presentation and short survival in case 2 is compatible with the other 10 patients reported previously. In this case metaphyseal chondrodysplasia was pronounced at birth. The radiological and clinical findings in our cases and previously reported patients with SCID and SLSD are summarised in table 1. Seven patients were reported from a workshop held in Albany, NY⁹ and only the results of skeletal and haematological findings are available. On review of table 1, it is apparent that severe shortening and bowing of the extremities in cases with SCID are not always associated with metaphyseal abnormalities. The onset of symptoms owing to immunodeficiency is usually soon after birth, with severe failure to thrive. The mean age at death of the reported patients was 5 months. Severe reduction in length at birth (> -2 SD) was reported in seven patients, bowing was present in six and absent in one. The most frequently reported metaphyseal abnormalities were of the costochondral junctions, with the radiological appearance of concave cupping and an ossification gap between the transverse processes and the ribs. These changes may be mild and appreciated only retrospectively.⁷ Metaphyseal abnormalities of the long bones were noted in 10 patients and consisted of flaring, irregularity, and thickening of the bone margins, unusually thick growth arrest lines, and areas of hypertranslucency. A relatively broad pelvis with short, flared ilia, long

horizontal acetabula, and small sacroiliac notches were reported in four patients. The interpedicular distances of the lumbosacral spine were normal (a caudal increase was reported in only one patient³). Mild platyspondyly was present in five patients.⁹ At necropsy genitourinary abnormalities were found in four patients and consisted of bilateral ureteric strictures at the ureteropelvic junction and cryptorchidism,³ hypospadias,⁶ and glomerular capillary mesangial proliferation.⁷ Our case 2 had dilated renal calyces. This patient also had generalised eczema and skin histology similar to that described by Gotoff *et al*⁵ in one case and Gatti *et al*⁶ in two sibs. It has been suggested that this may represent an ongoing degenerative process or a graft-versus-host reaction, which it resembles histologically.⁵

Sparsity of chondroblasts without orderly columnar formation has been reported.^{2 7 12} Cederbaum *et al*⁷ compared the bone histopathological findings in their three patients with SCID+ADA deficiency and SLSD with those of a patient with CHH. The authors noted complete absence of the normal transition of proliferating to hypertrophic chondrocytes in two cases with SCID+ADA deficiency. Only scattered hypertrophic cells with uninterrupted calcified cartilage formation were found, in their experience a unique finding in chondrodysplasias. Irregular columns of proliferating cells were seen in both our cases, but ADA levels were not determined. The aetiology of the defect affecting the skeletal and immune system in SCID and SLSD remains unknown. Polmar *et al*¹³ presented data supporting adenosine accumulation in a case with associated ADA deficiency as the primary cause of arrest in proliferation of the immune cells. A similar mechanism may cause arrest in chondrocyte proliferation.⁷ However, 23 patients with SCID and ADA deficiency seen to date at The Hospital for Sick Children, London (S Strobel, unpublished data) did not have similar skeletal abnormalities. Other additional pathogenic mechanisms must be operative to cause SLSD in the patients described. In the reported cases there are three sets of sibs, parental consanguinity, and a sex ratio of 7F:5M. These findings are compatible with autosomal recessive inheritance.

Ascertainment of associated ADA deficiency in the affected child and carrier status of the parents would allow prenatal diagnosis on amniotic fluid cells^{14 15} or chorionic villus biopsy in subsequent pregnancies. The shortening and bowing of the extremities may be mild and early detection by fetal ultrasound is unlikely.

In the differential diagnosis, disproportionate short stature and mild metaphyseal abnormalities may also be present in some patients with neutropenia and pancreatic insufficiency.¹⁶ Neutropenia and malabsorption with apparently progressive cellular immunodeficiency are known to exist in CHH.¹⁷ An

isolated case of pseudoachondroplasia with mild variable immunodeficiency has recently been reported by Kultursay *et al*¹⁸ and could be a chance observation.

The diagnosis of immunodeficiency with SLSD should be considered in infants and children with prenatal onset of disproportionate short stature, mild metaphyseal changes, and bowing of the long bones. This clinical entity should certainly be included in the WHO classification of immunodeficiencies.^{19 20} Children with SLSD and frequent infections should be investigated for underlying immunodeficiency and live vaccines should be withheld until the immune status is known.

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